

Case Report

Acute Tubulointerstitial Nephritis in a Patient Post-Renal Transplantation

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Abstract:

A 41-year old female patient who underwent kidney transplantation as an outcome of chronic glomerulonephritis came to the hospital with the signs of acute upper respiratory tract infection. As the patient further developed oliguria, peripheral edema, fever, and an increased BP, she was further relocated to the University Medical Center (UMC). Upon admission to UMC, signs of septic shock were detected, and acute transplant rejection was suspected, to exclude which kidney biopsy was performed and stage 3 chronic kidney disease (CKD) in allograft kidney was detected. Antibacterial treatment as well as pulse therapy were performed as patient had septic shock and tubulointerstitial nephritis (TIN).

Keywords: Acute Tubulointerstitial Nephritis; Renal Transplantation; Kidney Transplant Complications; Graft Dysfunction; Transplant Nephropathy; Immunosuppression; Biopsy Findings; Nephrology; Renal Pathology; Case Report

Introduction

Even though kidney transplantation is the definitive treatment for end-stage renal disease, complications such as rejection, infections, and drug toxicity are commonly observed in kidney transplant recipients. Due to the presence of immunosuppression, infections are of particular concern, as it can lead to allograft dysfunction (1, 2). 70% of patients after kidney transplantation are estimated to develop an infection in the first 3 years after transplantation (3). Consequently, infections are the leading cause of admission to the ICU for acute kidney injury (AKI) in kidney transplant patients (1). It is also the second leading cause of mortality in this patient group (3).

Based on the timeline of post-transplantation, the causative pathogens leading to infection differ. For instance, in the first month after the surgery, the source of infection is generally attributed to surgical complications, hospital-acquired infections, and pathogens derived from donors. On other hand, between 1 to 6 months after transplantation, urinary tract infections,

the reactivation of latent viruses and opportunistic infections are common. After 6 months, community acquired infections and the delayed presentation of viruses such as the CMV after the discontinuation of prophylaxis need to be considered (4).

Urinary tract infection (UTI), including pyelonephritis, is the most frequent bacterial infection encountered after kidney transplantation (5). Acute graft pyelonephritis is particularly concerning as it is the primary cause of systemic infection in KTRs. Studies have shown that pyelonephritis is especially noted in female patients and may contribute to permanent graft impairment (5).

Another important complication of infection in kidney transplant recipients is tubulointerstitial nephritis (TIN). It is a term that encompasses a group of inflammatory renal diseases that affect the filtration units of the kidney, typically sparing the glomeruli. Medications and infections are among the most common etiologies of tubulointerstitial nephritis. Additionally, TIN

is one of the major causes of renal transplant dysfunction. Allograft dysfunction from TIN is usually due to either bacterial pyelonephritis or BK viral infection. Due to the progression of TIN in a transplanted kidney, its lifespan can be significantly reduced as a consequence of permanent fibrosis (2). Considering the fact that TIN in renal transplant recipients is usually due to viral or bacterial infection, TIN in this patient population usually involves the reduction of immunosuppression, the administration of the antiviral cidofovir, and supportive care in the case of AKI (2).

Case Report

A 41-year old female with a history of chronic glomerulonephritis and subsequent kidney transplantation was admitted to the nephrology unit of University medical centre in a severe condition. The patient was first diagnosed with chronic tubulo-interstitial nephritis in 2018 after an acute viral upper respiratory tract infection, however serum creatinine level was not specified. However, a biopsy of the patient's native kidney was not previously performed before transplantation, thus the morphological diagnosis was not verified. Moreover, this is when the patient started experiencing headaches and a rise in her blood pressure up to 180/100 mm Hg. Her treatment included indapamide for blood pressure control. In January 2020 she was hospitalized to the nephrology department and diagnosed with Chronic nephritic syndrome, CKD stage 3, where she started receiving prednisolone 60 mg per day. Her CKD progressed from Stage 3 to Stage 5 in 2021, after which she started receiving hemodialysis. Such rapid development and progression of CKD to the terminal stage in the patient can be attributed to persistent arterial hypertension rise upto 180/100 mmHG, which was not treated properly due to poor antihypertensive therapy adherence. Also, this period coincides with the COVID pandemic, which can affect and worsen kidney function causing tubulointerstitial damage and can be related to the rapid worsening of patient's condition, however, according to patient's words he did not have COVID-19 history. As a result, in May 2022, she underwent kidney transplantation from a living donor. Post-transplantation, she received maintenance immunosuppression consisting of tacrolimus, mycophenolate mofetil, and prednisone. In December 2022 she received a pulse therapy with methylprednisolone, getting 500 mg on the first day of therapy and 250 mg on the following two days.

Nonetheless, in November 2023, the patient's condition deteriorated after an acute upper respiratory tract infection and she was admitted to a local hospital.

The following case study presents a kidney transplant recipient with acute kidney injury, pyelonephritis, and sepsis a year post-transplantation. While the patient's biopsy suggested acute tubulointerstitial nephritis, the patient was able to recover fully from her AKI and exhibited improved renal function. This case represents the complexity of managing immunosuppression in infection-triggered TIN in a post-transplant patient.

She had oliguria, peripheral edema, fever, and an increased BP. Moreover, hydronephrosis of the renal transplant was observed on imaging studies. Consequently, a ureteral stent was inserted to relieve any possible obstruction. Nevertheless, the patient remained in a severe condition. As a result, she was then transferred to UMC hospital for further management.

Upon admission, the patient was in a severe condition. Septic shock was suspected. Her creatinine was 399,2 $\mu\text{mol/L}$ (GFR of 12 ml/min) and BUN 18.2 mmol/L. Moreover, the patient had hyponatremia and metabolic acidosis. Hypervolemia was observed as the patient gained 22 kg. Her blood pressure dropped to 90/60 mm Hg. Her hemoglobin was 81.00 g/L, WBCs $23.61 \times 10^9/\text{L}$, and platelets $251 \times 10^9/\text{L}$. Her CRP was 89.56 mg/L, while procalcitonin constituted 1.03 ng/ml. Her urinalysis demonstrated proteinuria (1.56 g/L) and leukocyturia (500 cells/ μL). In addition, her urine culture depicted the presence of a high concentration of *Escherichia coli*. It was revealed that the patient had chronic hepatitis B infection (HBsAg of 4400 COI). Additionally, she had a decrease in the C3 and C4 complement levels, positive IgG and IgM levels toward anti-phospholipid antibodies, and weakly positive IgM antibodies toward β -2-glycoprotein-1. Her ANA panel was negative. After stabilizing the patient, to differentiate between the acute transplantation rejection and the recurrence of the disease, a kidney biopsy was performed. A chronic allograft nephropathy Stage 3 was established.

As the patient had sepsis and acute pyelonephritis, she was given an empirical antibiotic therapy of piperacillin/tazobactam and meropenem. Moreover, given that the patient had hyponatremia, azotemia, hypervolemia, and edema, it was decided to perform ultrafiltration. In addition, to control the patient's hypoalbuminemia and anemia, she received a transfusion of washed red blood cells (RBCs) and recormon 2,000 IU 3 times a week. Furthermore, to induce diuresis, IV furosemide was administered, which was slowly titrated to

subsequent combination of perioral furosemide and spironolactone combination. Further on, as gross hematuria and proteinuria was persisting and taking into account the patient's low complements and positive antibodies toward phospholipids, a pulse therapy with methylprednisolone was initiated starting from 500 mg and lowering to 250 mg. Subsequently, methylprednisolone was given PO with a dosage of 16 mg per day. During the hospitalization, the patient's tacrolimus serum levels reached 9 ng/ml, thus, she was maintained on tacrolimus (4 mg per day) and mycophenolic acid (720 mg per day) as a part of her immunosuppressive regime post-transplant.

Generally, the patient was also provided with a supportive therapy for her gastritis and arterial hyper-

tension. Moreover, hemostatic agents and systemic antifungal therapy were also initiated during the hospitalization.

At the time of discharge, the patient was in a stable clinical condition with no acute complaints. She did not exhibit any signs or symptoms of the infection. Moreover, her blood pressure remained relatively stable at approximately 125/80 mm Hg. Her weight significantly decreased with no peripheral edema noted. Spontaneous voiding was observed with an adequate balance of fluid intake and output. Moreover, her GFR improved up to 56.1 mL/min. On a subsequent planned hospitalization as a part of the patient's regular monitoring in July 2024, her GFR further increased to 76.3 mg/ml. Based on this progression, her diagnosis was revised to chronic allograft nephropathy Stage 2.

Discussion

A 41-year old female post renal transplantation was admitted to the hospital with AKI, pyelonephritis and sepsis for further management.

In this case, the patient's AKI and TIN were most likely the result of a combination of *E. coli* pyelonephritis, sepsis-induced hypoperfusion, and tacrolimus nephrotoxicity. UTIs, particularly in the setting of ureteral obstruction, remain a critical trigger for graft dysfunction in kidney recipients (5). Elevated tacrolimus levels (9 ng/mL) and increased infection susceptibility may have exacerbated renal injury. Appropriate management, including tacrolimus dose reduction to adjust the immunosuppression, was crucial in reversing AKI in our patient.

It is highly likely that the patient's *Escherichia coli*-associated pyelonephritis and sepsis resulted in the precipitation of her TIN. Urinary tract infections (UTIs), especially pyelonephritis, are the most common bacterial infections in KTRs and a leading cause of graft dysfunction (3). Additionally, the presence of ureteral obstruction and consequently hydronephrosis likely facilitated ascending infection. Acute interstitial inflammation due to bacterial TIN, compounded by hypoperfusion due to sepsis, might have led to AKI in the patient. It is noteworthy to mention that BK polyomavirus,

which is a common viral etiology of post-transplant TIN (3), was not observed in our patient, suggesting the need to exclude other opportunistic pathogens in post-transplant infections.

Furthermore, the patient's immunocompromised state could have rendered her susceptible to infection. The rigorous immunosuppressive regimen in kidney transplant recipients for the prevention of rejection can contribute to a high risk of infection, cancer, and cardiovascular disease (6). Thus, post-transplant patients must be on constant monitoring for dosage adjustment in immunosuppression to prevent the reduction of their allograft function as a consequence of these complications. The elevated concentration of tacrolimus (9 ng/ml) noted in our patient's blood during her hospital stay was indicative of excessive immunosuppression and could have contributed to the progression of her infection. Furthermore, tacrolimus is nephrotoxic (7) and can lead to acute nephropathy which is dose-dependent and reversible. It is triggered by renal vasoconstriction from vasoactive substances and can eventually cause acute kidney injury (AKI) (8). Thus, the adjustment of our patient's immunosuppressive regimen with tacrolimus was an essential step in her management.

Conclusion

This case highlights the significance of strict supervision of patients following renal transplantation. Due to being in an immunosuppressive state, they are susceptible to infections, which can trigger rejection or other renal complications. Here we have presented a

case of a post-transplantation patient who regained renal function after acute kidney injury following sepsis and pyelonephritis.

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Original Article

Population-Based Screening during World Kidney Day in Kazakhstan: Prevalence and Risk Factors of Reduced Renal Function

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Abstract:

Background: Chronic kidney disease (CKD) is a major global health challenge, yet population-based data from Central Asia are scarce. We conducted a population-based screening study to assess kidney function distribution and associated risk factors in Astana, Kazakhstan.

Methods: In March 2024, 636 adults were screened through convenience sampling at four major institutions in Astana. After excluding incomplete data, 569 participants were analyzed. Demographic, lifestyle, and clinical information were collected, and serum creatinine was used to estimate glomerular filtration rate (eGFR). Reduced renal function was defined as eGFR <90 mL/min/1.73 m². Group comparisons and logistic regression analyses were performed to identify risk factors for reduced renal function.

Results: The median age of participants was 46 years (IQR 33–55), and 79.8% were women. Median eGFR was 92.8 (IQR 79.8–111.3) mL/min/1.73 m²; 54.1% had eGFR ≥90, 42.4% had eGFR 60–89, and 3.5% had eGFR 45–59. Reduced renal function was more common among older adults, females and those with hypertension and heart failure. In multivariable analysis, older age and female sex were independent predictors of reduced renal function. Awareness was low: only 15.0% of individuals with eGFR 45–59 reported having CKD.

Conclusion: This study provides the population-based evidence on kidney function in Astana, Kazakhstan. Reduced renal function was common, particularly among older adults. Findings highlight the importance of population-based screening and targeted prevention strategies to address kidney health in Kazakhstan.

Keywords: Chronic Kidney Disease; Screening; Awareness; Kazakhstan; Central Asia

Introduction

Chronic kidney disease (CKD) is a major global health challenge, affecting over 10% of the worldwide population, with prevalence rising sharply over recent decades – an increase of approximately 92% between

1990 and 2021 (1-3). This progressive chronic condition substantially increases risks of cardiovascular events,

premature mortality, and health system costs, particularly when patients present at advanced stages requiring renal replacement therapy (4,5).

Early detection of CKD is therefore essential. Timely intervention can slow disease progression, improve patient outcomes and reduce treatment costs (6). Yet, CKD is often asymptomatic in its early stages, leading to frequent underdiagnosis until significant kidney damage has occurred. Population-based screening using estimated glomerular filtration rate (eGFR) and albuminuria assessment has proven effective for identifying CKD early (7). However, screening strategies must be appropriately evaluated for cost-effectiveness, especially in resource-constrained settings where healthcare budgets are limited and competing priorities are high. Reliable prevalence data form a crucial component of this evaluation, as they provide the foundation for estimating disease burden, projecting healthcare needs, and assessing the potential value of implementing systematic screening programs (8).

Epidemiological studies have shown considerable variation in the prevalence of CKD across countries and regions, influenced by demographic, lifestyle, and healthcare factors (9). Central Asia is notably underrepresented in the current literature, with limited population-based data on kidney health. In Kazakhstan, an upper-middle income country located in Central Asia, only one nationally representative study has

assessed CKD prevalence. It included 6,720 adults and reported that 25.2% had eGFR of 60–89 mL/min/1.73 m², indicating a large reservoir of early kidney impairment (10). While this study provides valuable insights, it represents the sole source of population-based prevalence data in the country. Some studies have attempted to estimate prevalence from national registry data; however, such estimates are likely to underestimate the true burden of CKD (11,12). Accordingly, further research is essential to generate more comprehensive and region-specific evidence on CKD burden in Kazakhstan and the wider Central Asian region, especially given the fact that the burden of CKD in Kazakhstan is expected to increase in the future (11), while national health system preparedness remains limited (13,14).

To address this evidence gap, this population-based screening study was conducted in Astana, Kazakhstan, as part of the World Kidney Day campaign. The primary objective of this study was to determine the prevalence of reduced renal function in a general adult population of Astana. Secondary objective was characterizing the sociodemographic and clinical risk factor profiles associated with reduced renal function. The findings are intended to inform healthcare policy development, guide resource allocation decisions, and contribute to the growing body of evidence supporting early detection and management of CKD in Central Asian populations.

Methods

Study Design: This was a population-based, cross-sectional screening study conducted to assess kidney function distribution and the prevalence of reduced eGFR in Astana, Kazakhstan. The study design followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies (15).

Participant Selection: The study was conducted in Astana, the capital city of Kazakhstan on March 14, 2024. Participants were recruited through convenience sampling from four major institutions: National Research Center for Maternal and Child Health, Republican Diagnostic Center, National Scientific Cardiac Surgery Center, and Nazarbayev University Health Center. Participant recruitment involved approaching passersby at these four strategic locations. A total of 636 adults were successfully enrolled in the study. Adults aged 18 years and older, who were residents of Kazakhstan, able to provide informed consent and had willingness to participate were included. The criteria for exclusion were having an acute illness at the time of screening, pregnancy and inability provide informed consent.

Data Collection & Variables: The following data was collected from the participants:

Sociodemographic Variables: Age, sex, educational attainment, occupation, and residence (urban vs. rural).

Lifestyle factors: Smoking status (categorized as non-smoker, <1 pack/day, >1 pack/day) and alcohol consumption patterns (frequency).

Medical history: Participants were asked whether they believed they have CKD to assess their self-awareness of kidney health status. Additionally, history of comorbid conditions (history of hypertension, diabetes, cardiovascular disease, heart failure, and stroke) were assessed by self-report.

Laboratory/Clinical Methods: Blood pressure (measured using standardized protocols with participants in a seated position after at least 5 minutes of rest), height and weight were measured. Body mass index (BMI) was calculated by dividing weight in kg by height in m².

Serum creatinine and urinary microalbumin was measured using standardized laboratory methods. The normal albumin concentration is considered less than

20 mg/L and more than 200 mg/L is considered macroalbuminuria (16). The CKD-EPI equation (17) was used to calculate eGFR from serum creatinine. The CKD-EPI 2021 equation was used, which does not incorporate race as a factor.

Participants were classified into eGFR categories (≥ 90 , 60–89, 45–59, 30–44, 15–29, <15 mL/min/1.73 m²) for descriptive stratification of kidney function. Because chronicity (≥ 3 months) and albuminuria quantified by albumin-to-creatinine ratio (ACR) were not available, these categories were used solely to describe cross-sectional kidney function and do not constitute CKD diagnoses or staging.

Statistical Analysis: Of the 636 adults initially screened, data were incomplete for 67 individuals. The pattern of missingness was assessed using Little's MCAR test. The missingness was consistent with being missing completely at random (MCAR) ($p = 0.419$). Therefore, a complete-case analysis was performed, and 569 participants were retained in the final dataset.

Descriptive statistics were computed for all variables. Normally distributed continuous variables were presented as mean $\pm$ standard deviation, while non-normally distributed variables were expressed as median with interquartile range (IQR). Categorical variables were reported as counts and percentages. Group comparisons were conducted using the chi-square test for categorical variables. For continuous variables, Student's t-test was applied when normality assumptions

were met, and the Wilcoxon rank-sum test (Mann-Whitney U test) was used for non-normally distributed variables. For comparisons across more than two groups, one-way analysis of variance (ANOVA) or the Kruskal-Wallis test was applied as appropriate.

Categorization by eGFR was reported overall and by stage. For regression analysis, the outcome was defined as reduced renal function, coded as a binary variable using an eGFR threshold of <90 mL/min/1.73 m². Unadjusted and adjusted logistic regression models were used to examine associations between reduced renal function and potential risk factors. Results were presented as odds ratios (OR) with 95% confidence intervals (CI). A p-value <0.05 was considered statistically significant.

All analyses were performed in Stata (version 16.0; StataCorp, College Station, TX, USA). A p-value <0.05 was considered statistically significant.

Ethical Considerations: The study was conducted in accordance with the Declaration of Helsinki and local ethical guidelines. All process was performed after the approval of the Ethics Committee of CF "University Medical Center" in Astana, Kazakhstan (reference number 2024/02-38). Written informed consent was obtained from all participants before enrollment. Participants with abnormal findings were advised to seek appropriate medical follow-up.

Results

Participant characteristics: The final analytic sample consisted of 569 participants, including 115 (20.2%) men and 454 (79.8%) women, with a median age of 46 years (IQR: 33–55). Women were significantly older than men (median age 47 vs. 40 years, $p < 0.001$). The majority of participants reported higher education ($\geq$ bachelor's degree: 45.0%) and urban residence (91.6%). More than half were employed in medicine or pharmaceuticals (55.4%). The prevalence of self-reported CKD was 13.0%, with no significant sex difference ($p = 0.767$). Hypertension and diabetes mellitus were reported by 24.3% and 8.1% of participants, respectively. Median systolic blood pressure was higher in men than women (120 vs. 110 mmHg, $p < 0.001$). Also, men had significantly higher eGFR values compared with women (109.1 vs. 89.8 mL/min/1.73 m², $p < 0.001$). Urinary microalbumin was measured in all participants, and concentrations were uniformly <0.3 mg/L, with a median of 0.07 mg/L (IQR: 0.05–0.09) indicating

absence of albuminuria in this cohort. Detailed characteristics of participants stratified by gender are provided in Table 1.

Kidney Function Distribution: The median eGFR in the cohort was 92.8 mL/min/1.73 m² (IQR: 79.8–111.3). Of the total, 308 participants (54.1%) had eGFR ≥ 90 mL/min/1.73 m², 241 (42.4%) had eGFR 60–89, and 20 (3.5%) had eGFR 45–59. No participants had eGFR <45 . Participants with lower eGFR were significantly older (median age 64 years for eGFR 45–59 vs. 34 years for eGFR ≥ 90 , $p < 0.001$). Lower eGFR was also associated with more frequent self-report of hypertension (70.0% in eGFR 45–59 vs. 14.3% in ≥ 90 , $p < 0.001$) and heart failure (20.0% vs. 3.6%, $p = 0.002$). BMI and systolic blood pressure were progressively higher with declining eGFR ($p < 0.001$ for both). Among participants with preserved kidney function (eGFR ≥ 90), 11.7% reported knowing they had CKD. Awareness of CKD status was low across participants with reduced renal function - 14.5% and 15.0% in those with eGFR 60–89 and eGFR 45–59, respectively (Table 2).

Table 1. Sociodemographic and Clinical Characteristics of Participants by Gender

Characteristic	Total (n=569)	Men (n=115)	Women (n = 454)	p-value
Age - years, median (IQR)	46 (33–55)	40 (29-52)	47 (35-56)	<0.001**
Education (bachelor's and higher), n (%)	256 (45.0)	66 (57.4)	190 (41.9)	0.003*
Occupation , n (%)				<0.001**
Industrial production	17 (3.0)	13 (11.3)	4 (0.9)	
Trade/Sales	16 (2.8)	5 (4.4)	11 (2.4)	
Science/Education	31 (5.5)	12 (10.4)	19 (4.2)	
Civil service	24 (4.2)	5 (4.4)	19 (4.2)	
Transport/Logistics	8 (1.4)	7 (6.1)	1 (0.2)	
Medicine/Pharmaceuticals	315 (55.4)	31 (27.0)	284 (62.6)	
Other	102 (17.9)	29 (25.2)	73 (16.1)	
Unemployed	56 (9.9)	13 (11.3)	43 (9.5)	
Residence , n (%)				0.388
Urban	521 (91.6)	103 (89.6)	418 (92.1)	
Rural	48 (8.4)	12 (10.4)	36 (7.9)	
Smoking , n (%)				<0.001**
No	540 (94.9)	90 (78.3)	450 (99.1)	
Yes, < 1 pack/day	24 (4.2)	20 (17.4)	4 (0.9)	
Yes, > 1 pack/day	5 (0.9)	5 (4.4)	0 (0.0)	
Alcohol , n (%)				<0.001**
Never	408 (73.0)	61 (54.5)	347 (77.6)	
Every month	37 (6.6)	19 (17.0)	18 (4.0)	
Every week	5 (0.9)	3 (2.7)	2 (0.5)	
Every day	1 (0.2)	1 (0.9)	0 (0.0)	
Other	108 (19.3)	28 (25.0)	80 (17.9)	
CKD – yes, n (%)	74 (13.0)	14 (12.2)	60 (13.2)	0.767
“Have you ever been diagnosed with hypertension” – yes, n (%)	138 (24.3)	24 (20.9)	114 (25.1)	0.343
“Have you ever been diagnosed with DM” – yes, n (%)	46 (8.1)	8 (7.0)	38 (8.4)	0.619
“Have you ever been diagnosed with acute/chronic HF” - yes, n (%)	36 (6.3)	9 (7.8)	27 (6.0)	0.460
Stroke - yes, n (%)	14 (2.5)	3 (2.6)	11 (2.4)	0.909
SBP , median (IQR)	115 (105–125)	120 (110-130)	110 (100-120)	<0.001**
BMI , median (IQR)	25.6 (22.6–29.4)	26.3 (22.2–29.4)	25.5 (22.7–29.4)	0.901
eGFR , median (IQR)	92.8 (79.8–111.3)	109.1 (86.5–122.7)	89.8 (78.6-107.1)	<0.001**
Microalbumin , median (IQR)	0.07 (0.05-0.09)	0.07 (0.05-0.1)	0.07 (0.05-0.09)	0.610

Note: BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus, eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; SBP, systolic blood pressure.

*p-value < 0.05

**p-value < 0.001

Table 2. Participant Characteristics by eGFR Category.

Characteristic	eGFR category, ml/min/1.7 m ²			p-value
	>90 (n=308)	60-90 (n=241)	45-60 (n=20)	
Age - years, median (IQR)	34 (28-42)	55 (50-60)	64 (58.5-71)	<0.001**
Gender – male, n (%)	82 (26.6)	30 (12.5)	3 (15.0)	<0.001**
Education – bachelor's and higher, n (%)	172 (55.8)	81 (33.6)	3 (15.0)	<0.001**
Occupation – medicine/pharmaceuticals, n (%)	171 (55.6)	133 (55.2)	11 (55.0)	0.996
Residence – urban, n (%)	20 (6.5)	26 (10.8)	2 (10.0)	0.193
"Have you ever been diagnosed with CKD" – yes, n (%)	36 (11.7)	35 (14.5)	3 (15.0)	0.597
"Have you ever been diagnosed with CKD" – yes, n (%) (only among medicine/pharmaceuticals workers)	13 (7.6)	16 (12.0)	1 (9.1)	0.426
"Have you ever been diagnosed with hypertension" - yes, n (%)	44 (14.3)	80 (33.2)	14 (70.0)	<0.001**
"Have you ever been diagnosed with DM" - yes, n (%)	19 (6.2)	25 (10.4)	2 (10.0)	0.190
"Have you ever been diagnosed with acute/chronic HF" - yes, n (%)	11 (3.6)	21 (8.71)	4 (20.0)	0.002*
Stroke - yes, n (%)	4 (1.3)	9 (3.73)	1 (5.0)	0.142
SBP, median (IQR)	111.4 (17.2)	120.8 (18.0)	130.5 (17.0)	<0.001**
BMI, median (IQR)	24.5 (21.4-28.5)	26.7 (24.1-30.3)	29.1 (22.6-29.5)	<0.001**
Microalbumin, median (IQR)	0.05 (0.04-0.07)	0.09 (0.07-0.1)	0.15 (0.11-0.2)	<0.001**

Note: BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus, eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; SBP, systolic blood pressure.

*p-value < 0.05

**p-value < 0.001

Regression Analysis: Figure 1 illustrates the linear relationship between age and eGFR stratified by sex. Both men and women demonstrated a progressive decline in eGFR with increasing age. Across the age spectrum, men consistently had higher predicted eGFR values compared with women, although the rate of decline was similar in both sexes.

In unadjusted logistic regression models, older age, female sex, higher BMI, higher blood pressure,

lower education, and history of heart failure were significantly associated with higher odds of reduced kidney function. After adjustment, independent predictors of lower eGFR were older age (OR 1.34 (1.26 to 1.41), $p < 0.001$) and female sex (male vs. female OR 0.29 (0.12 to 0.71), $p = 0.007$). Notably, after adjustment, BMI exhibited an inverse association with reduced kidney function (OR 0.93 (0.87 to 0.99), $p = 0.029$). Education, systolic blood pressure, and history of heart failure were not significant in the multivariable model (Table 3).

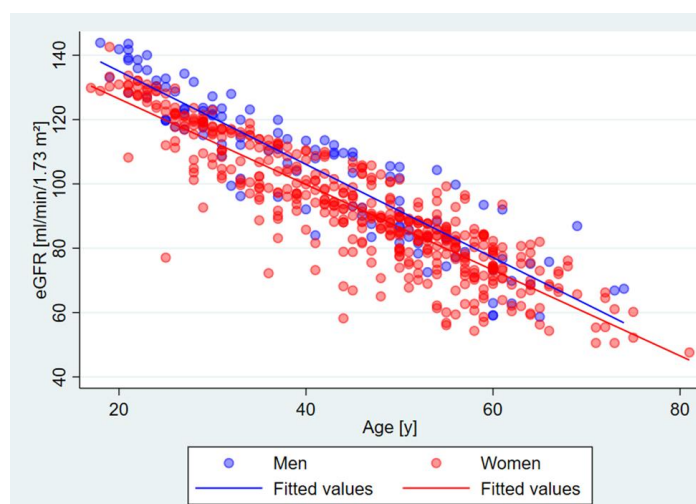


Figure 1. Linear regression of age and estimated glomerular filtration rate stratified by sex. Both men (blue line) and women (red line) showed a progressive decline in eGFR with advancing age, with men consistently having higher eGFR values.

Table 3. Logistic Regression Analysis of Factors Associated with Reduced Renal Function.

Participant's characteristic	Unadjusted model OR (95% CI)	p-value	Adjusted model OR (95% CI)	p-value
Age	1.31 (1.25 to 1.37)	<0.001**	1.34 (1.26 to 1.41)	<0.001**
Gender - male	0.39 (0.25 to 0.62)	<0.001**	0.29 (0.12 to 0.71)	0.007*
Education – bachelor's and higher	0.38 (0.27 to 0.53)	<0.001**	1.17 (0.60 to 2.27)	0.645
"Have you ever been diagnosed with acute/chronic HF" - yes	2.86 (1.38 to 5.93)	0.003*	0.52 (0.14 to 1.83)	0.306
"Have you ever been diagnosed with acute/chronic CKD" – yes	1.29 (0.79 to 2.10)	0.311	0.54 (0.22 to 1.33)	0.184
SBP	1.03 (1.02 to 1.04)	<0.001**	1.01 (0.99 to 1.03)	0.280
BMI	1.08 (1.04 to 1.12)	<0.001**	0.93 (0.87 to 0.99)	0.029*

Note: BMI, body mass index; CI, confidence interval; HF, heart failure; SBP, systolic blood pressure.

*p-value < 0.05

**p-value < 0.001

Discussion

This population-based screening study provides important insights into kidney function distribution and CKD awareness in Kazakhstan.

Prevalence and Distribution of Reduced Renal Function: The high prevalence of reduced renal function observed in our study is consistent with regional trends reported in Kazakhstan's national surveillance

data. In our study, 45.9% of participants had eGFR below 90 mL/min/1.73 m², which is higher than the 25.2% reported by Nursultanova et al. (2023) (10). This large difference likely reflects an older and predominantly female sample and non-probability recruitment in healthcare facilities. The strong age-related decline in kidney function is observed in our cohort with participants having eGFR 45-59 mL/min/1.73 m² being significantly older (median 64 years) than those with preserved function (median 34 years). This age-stratified pattern is consistent with previous studies from Kazakhstan and globally, emphasizing the importance of age as a primary determinant of kidney function decline (10,18). The absence of stage 4-5 CKD (eGFR <30 mL/min/1.73 m²) in our screening cohort is consistent with global stage-specific prevalence (stage 4 ~0.4%, stage 5 ~0.1%) (9), making zero observed cases plausible given sampling variability and the cohort's relatively young median age (18).

Interestingly, no participants demonstrated microalbuminuria, as urinary albumin concentrations were uniformly <0.3 mg/L. However, interpretation is limited by the use of raw urinary microalbumin concentration rather than albumin-to-creatinine ratio, which is the recommended standard due to variability from urine dilution. Nonetheless, the absence of albuminuria supports our conclusion that reduced eGFR was the predominant renal abnormality observed in this sample.

Risk Factor Profile and Associations: The independent association between older age and female sex with higher odds of reduced renal function in our multivariable analysis supports global patterns (19). The large between-sex difference in median eGFR (109.1 mL/min/1.73 m² in men vs. 89.8 mL/min/1.73 m² in women) may partly reflect men's younger age distribution and the sample's educational differences, both of which can influence creatinine-based eGFR through age- and muscle-mass-related effects and health behavior patterns (20,21).

Although higher BMI and systolic blood pressure showed association with higher odds of reduced renal function in unadjusted analyses, the blood pressure's association lost statistical significance after adjustment for age, sex, and comorbidities. Whereas, the reversal of BMI's association after adjustment should be interpreted as a modeling artifact driven by outcome dichotomization, nonlinearity around the eGFR threshold, and confounding/suppression by age and sex, rather than evidence that higher BMI is protective; the descriptive increase in BMI with declining eGFR supports this caution. Indeed, elevated adiposity and blood pressure

remain recognized risk factors for CKD onset and progression, and their attenuation here likely reflects shared pathways and collinearity with other factors rather than absence of effect (19).

CKD Awareness and Challenge of Limited Health Literacy: One of the important findings of our study is the low CKD awareness among those who have it. Only 15.0% of those with CKD Stage 3 (eGFR 45-59 mL/min/1.73 m²) were aware of their condition. However, this estimate may still be overestimated because 11.7% of participants with normal kidney function (eGFR ≥90 mL/min/1.73 m²) reported having CKD, indicating substantial bias in self-reported diagnoses and suggesting true awareness among those with reduced renal function is even lower. The disconnect between objective kidney function and subjective CKD awareness in our study reflects broader challenges in health communication and medical literacy. In primary care clinics of Almaty, another large city in Kazakhstan, 45.5% of adults had limited health literacy, indicating substantial difficulty accessing, understanding, appraising, and applying health information in routine care contexts (22). This magnitude of limited literacy can plausibly lead to confusion between CKD and other kidney/urinary conditions, inflating self-reported CKD among people with normal eGFR and masking true awareness among those with reduced function. Regional evidence supports low CKD awareness: a 10-country survey across former Soviet states (n=2,715) documented limited public knowledge of kidney functions and CKD recognition (23). Within the subgroup employed in medicine/pharmaceuticals, awareness among those with Stage 3 CKD was only 9.1%, even lower than in the overall sample, which likely reflects more accurate understanding of what constitutes CKD rather than truly lower awareness; this pattern reinforces that misclassification inflates self-reported CKD in the general cohort.

Strengths and Limitations: This study has several strengths. First, it provides region-specific evidence on kidney function in Astana, addressing a major data gap for Central Asia and complementing limited national estimates from Kazakhstan. Second, concurrent collection of sociodemographic and clinical information enabled us to clarify potential confounding and shared pathways. Third, parallel reporting of self-reported CKD versus objectively measured eGFR reveals substantial misperception, quantifying information bias relevant to screening and education strategies.

Several limitations must be acknowledged in interpreting our findings. Our convenience sampling

approach and recruitment from major healthcare institutions may have introduced selection bias, potentially overrepresenting health-conscious individuals or those with worse health. The lack of albuminuria assessment and the cross-sectional nature of our study mean we cannot definitively diagnose CKD according to standard criteria requiring persistence of abnormalities for at least three months. The reliance on self-reported comor-

bidities and CKD awareness introduces potential information bias, as demonstrated by our awareness findings. However, this limitation itself provides valuable insights into the challenges of using self-reported health data in research and clinical practice in this population. Additionally, albuminuria assessment was limited to spot urinary albumin concentration without a creatinine correction or 24 hours urine collection, which may underestimate the prevalence of early kidney damage.

Conclusion

This study provides valuable insights into kidney function distribution and CKD awareness in Kazakhstan, contributing to the limited epidemiological data from Central Asia. While our findings show kidney function patterns consistent with regional trends, they reveal concerning gaps in CKD awareness that may compromise early detection and management efforts. Our findings emphasize the critical importance of im-

proving health literacy, enhancing clinical communication, and developing targeted education programs to address the growing burden of CKD in Kazakhstan and the broader Central Asian region. Understanding and addressing these awareness biases will be essential for implementing effective CKD prevention and management strategies in resource-constrained healthcare settings.

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Ethics approval: The study was conducted in accordance with the Declaration of Helsinki and local ethical guidelines. All process was performed after the approval of the Ethics Committee of CF "University Medical Center" in Astana, Kazakhstan (reference number 2024/02-38). Written informed consent was obtained from all participants before enrollment. Participants with abnormal findings were advised to seek appropriate medical follow-up.

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Case Report

AA-Amyloidosis in an Adolescent with Familial Mediterranean Fever: A Case ReportSaltanat Rakhimzhanova¹, Galiya Shaimardanova², Aigerim Smagulova², Aidana Nalibek¹¹Department of Nephrology and Dialysis, University Medical Center, Astana, Kazakhstan²Department of Pathomorphology, National Scientific Medical Center, Astana, Kazakhstan**Abstract:**

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Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disorder caused by mutations in the MEFV gene. It is most common among populations from the Eastern Mediterranean region, including Turks, Armenians, Arabs, and Sephardic Jews. One of the most serious complications of FMF is AA amyloidosis, which develops as a result of chronic inflammation and the deposition of serum amyloid A protein. AA amyloidosis frequently affects the kidneys, leading to nephrotic syndrome and chronic kidney disease.

We report a case of a 17-year-old Turkish male presenting with recurrent episodes of fever, joint pain, periodic skin rashes, and intermittent hypertension. Laboratory evaluation revealed nephrotic-range proteinuria, hypoalbuminemia, low serum IgG, and elevated inflammatory markers. Renal biopsy confirmed AA amyloidosis with moderate interstitial lymphocytic infiltration and mild fibrosis. Genetic testing identified a homozygous pathogenic variant in exon 10 of the MEFV gene (p.Met694Val), previously reported and strongly associated with FMF.

This case highlights the rarity of such presentations and emphasizes the importance of early diagnosis of FMF complicated by AA amyloidosis. The patient remains on colchicine therapy with careful monitoring for potential complications; corticosteroids were gradually tapered following confirmation of amyloidosis, with supportive and symptomatic management continued.

Keywords: Familial Mediterranean Fever; Secondary amyloidosis (AA); MEFV protein; nephrotic syndrome; renal biopsy

Introduction

AA amyloidosis is a systemic disease characterized by extracellular deposition of fibrils derived from serum amyloid A protein, primarily affecting the kidneys and leading to nephrotic syndrome and renal failure (1,2). Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease and the leading cause of AA amyloidosis in many regions (3-5). It is caused by mutations in the MEFV gene, particularly in exon 10, such as the p.Met694Val variant, associated with severe disease and amyloid risk (6,7).

Although FMF predominantly affects populations around the Mediterranean basin-Turks, Armenians, Arabs, and Jews-cases have been increasingly reported outside endemic areas (3,4). In Central Asia, including Kazakhstan, FMF is rarely diagnosed, often due

to limited awareness and the nonspecific presentation of early symptoms. Studies indicate that initiating colchicine therapy early in FMF patients can lower the risk of developing amyloidosis, even before any signs of kidney complications appear (8).

Renal biopsy remains the cornerstone for diagnosing AA amyloidosis, confirming amyloid type, and guiding management (9). Early detection and targeted anti-inflammatory therapy, primarily colchicine, have been proven to reduce amyloid deposition and improve prognosis (10). Our case represents one of the first documented biopsy-proven FMF-related AA amyloidosis cases in Kazakhstan, emphasizing the diagnostic challenges and the necessity of early morphological verification in atypical clinical scenarios.

Case Report

The patient, a 17-year-old male of Turkish ethnicity, was admitted to the nephrology department with complaints of lower limb edema, decreased urine output (diuresis), knee joint pain with restricted mobility, and limping. The complaints were accompanied by intermittent fever reaching 38–40 °C. During febrile episodes, hemorrhagic rashes and occasional purpuric lesions on the skin of the shins and thighs were noted, which disappeared upon normalization of temperature. Episodes of arterial hypertension (AH) alternating with hypotension were also recorded. On physical examination: height-168.5 cm, body weight -46.5 kg, body temperature -36.4 °C, edema of the shins, urine output (diuresis)-up to 2000 ml/day, gross hematuria (macroscopic blood in urine) was not observed. Laboratory tests at admission: hemoglobin (Hb) -107 g/dL, erythrocyte sedimentation rate (ESR) -57 mm/h, C-reactive protein (CRP)- 33.9 mg/L, urea -4.2 mmol/L, creatinine (Cr) -63.9 µmol/L, albumin -17.6 g/L, total protein -43.0 g/L. Immunogram: immunoglobulin M (IgM) -2.04 g/L, immunoglobulin G (IgG) - 3.99 g/L, immunoglobulin A (IgA) -1.42 g/L, rheumatoid factor (RF) -7.5 IU/mL. Immunological markers: antinuclear antibodies (ANA) negative (1:80), anticardiolipin antibodies (IgG, IgM) within normal range, anti-double-stranded DNA antibodies (anti-dsDNA), extractable nuclear antigens (ENA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane antibodies (anti-GBM) — negative. QuantiFERON test and GeneXpert were negative. Blood and urine cultures showed no growth. Urinalysis (UA) revealed proteinuria of 4.4 g/L. Renal ultrasound: right kidney — 123 × 49 mm, parenchyma 18 mm; left kidney — 129 × 55 mm, parenchyma 8 mm. X-ray of the knee joints: no bone-destructive changes, signs of arthritis. The patient was preliminarily diagnosed with primary steroid-resistant nephrotic syndrome of high activity. However, during hospitalization, a single episode of gross hematuria and episodes of arterial hypertension complicated the diagnostic process. Genetic analysis prior to renal biopsy results revealed a pathogenic homozygous variant MEFV p.M694V (rs61752717), typical for autosomal recessive familial Mediterranean fever (FMF). Additionally, a heterozygous variant of uncertain significance, LAMA5 p.His2445Tyr (rs200433384), was identified. Renal biopsy results showed morphological features of amyloid nephrosis with mild fibrosis and focal moderate lymphocytic infiltration in the interstitial tissue. All nine glomeruli contained massive extracellular amyloid deposits, moderate mesangial proliferation, thickening and lobularity of the basement membrane,

and connective tissue adhesions. In the tubular epithelium — hyaline-droplet and hydropic degeneration, lipid inclusions, erythrocytes. Amyloid deposits were also present in the stroma and medium- to small-caliber vessels (Figure 1). Masson's trichrome histochemical staining demonstrated amyloid protein masses in all glomeruli, stained orange-blue (Figure 2). Congo red staining for amyloid was positive in six glomeruli, on the tubular basement membrane, stroma, and vessels, appearing orange-brown (Figure 3). AA amyloidosis of the kidneys on the background of autosomal recessive FMF was confirmed. Before renal biopsy results, treatment was initiated for nephrotic syndrome, single gross hematuria, and arterial hypertension: hydroxychloroquine (5 mg/kg, 300 mg/day), pulse therapy with methylprednisolone (750 mg × 3), followed by oral administration of 48 mg/day, and anakinra (100 mg × 2). Symptomatic therapy included albumin, immunoglobulin, calcium carbonate, diuretics, and antihypertensive drugs. After confirmation of AA amyloidosis and genetic analysis, glucocorticoids were gradually discontinued, and colchicine therapy (3 mg/day) was continued. After 2 months, the patient's condition: estimated glomerular filtration rate (eGFR) -100 mL/min, CRP decreased to 5.68 mg/L, albumin -31.82 g/L, total protein -52.24 g/L with ongoing replacement therapy. Clinical Course Table – see (Figure 4).



Figure 1. Immunofluorescence: Weak lambda light chain fluorescence observed in glomerular capillary loops, along the basement membrane, and in tubular epithelium. ×400.

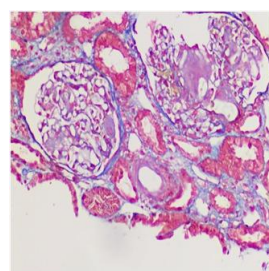


Figure 2. Segmental amyloid deposits in glomerular capillary loops and vascular walls, stained bluish-pink. Masson's trichrome staining, ×100.

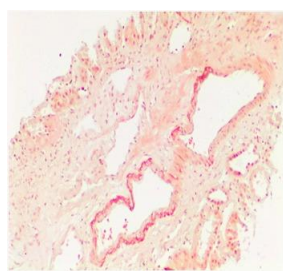


Figure 3. Pathological protein deposition in vascular walls showing orange-red coloration. Congo red staining for amyloid, $\times 400$.

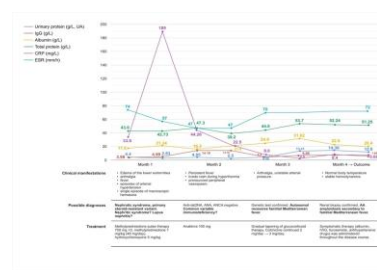


Figure 4. Clinical course of the patient during hospitalization. ESR – erythrocyte sedimentation rate (mm/h), CRP – C-reactive protein (mg/L), Total protein – total protein (g/L), Albumin – albumin (g/L), IgG – immunoglobulin G (g/L), Urinary protein (UA) – proteinuria in urinalysis (g/L), Anti-dsDNA – antibodies to double-stranded DNA, ANA – antinuclear antibodies, ANCA – antineutrophil cytoplasmic antibodies, IVIG – intravenous immunoglobulin.

Discussion

The goal of this case report is to underscore the clinical importance of recognizing FMF-related AA amyloidosis early, especially in regions where the disease is not endemic (1). Persistent subclinical inflammation due to unrecognized FMF can lead to irreversible renal damage (2). Early histopathological confirmation through renal biopsy enables appropriate treatment and prognosis assessment (1).

Historical cohorts have demonstrated that uncontrolled FMF with elevated SAA levels inevitably progresses to AA amyloidosis if untreated (5). Our diagnostic approach combined clinical symptoms, biochemical findings, and genetic testing with renal histology—aligning with recommendations from Ozen et al. and Lachmann et al. (5). The Congo red staining with characteristic apple-green birefringence under polarized light, and immunofluorescence confirming AA-type deposits, established the diagnosis (9).

Renal biopsy provided crucial diagnostic clarity by differentiating amyloidosis from other glomerulopathies, particularly in patients presenting with nephrotic-range proteinuria and hypertension (9). This morphological confirmation directly impacted clinical decisions—allowing de-escalation of glucocorticoids and continuation of colchicine therapy (10).

Conclusion

This case highlights a rare instance of FMF-associated AA amyloidosis in Kazakhstan, demonstrating the vital role of early histological verification, genetic testing, and anti-inflammatory management. Colchicine remains the first-line therapy, while IL-1 blockade

Colchicine remains the cornerstone of FMF therapy, preventing inflammatory attacks and amyloid deposition (10,11). In colchicine-resistant or intolerant patients, IL-1 inhibitors such as anakinra or canakinumab have shown efficacy in reducing inflammation and stabilizing renal function (11,12). Our patient responded well to colchicine monotherapy, maintaining remission and stable renal function without requiring biologics, consistent with published outcomes (13).

Compared with cases from endemic regions, this patient's delayed diagnosis and atypical presentation in Kazakhstan underline the geographic gap in awareness. Similar cases described by Yamada et al. (3) and Demirkaya et al. (5) also reported amyloidosis as the first clinical manifestation of FMF, reinforcing the need for genetic and histological evaluation in atypical nephrotic syndromes.

We recommend that clinicians in Central Asia include FMF in the differential diagnosis of unexplained nephrotic syndrome and hypertension in young patients. Early genetic testing and renal biopsy are critical for preventing irreversible organ damage (9). Close monitoring of SAA levels is also advised to evaluate inflammatory control (9,10).

offers an option for refractory cases. Kidney transplantation outcomes in FMF-related amyloidosis remain insufficiently studied and warrant further investigation (13).

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Study of the Prevalence and Risk Factors of Chronic Kidney Disease in the Kyrgyz Republic

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Abstract:

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Background: Chronic kidney disease (CKD) is an increasing global health concern and a major contributor to cardiovascular morbidity and mortality. Although its global prevalence is estimated at about 13%, data from Central Asia are limited.

Objective: To assess the prevalence, structure, and key determinants of CKD among adults in the Kyrgyz Republic.

Methods: A population-based cross-sectional study was conducted among adults aged ≥ 18 years across different regions. CKD was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² and/or a urinary albumin-to-creatinine ratio (UACR) ≥ 30 mg/g. Disease severity was staged by eGFR and albuminuria categories. Logistic regression identified independent predictors of CKD.

Results: The overall CKD prevalence was 10.8%, comparable to global estimates. Prevalence increased with age, reaching 25.0% among participants ≥ 70 years, of whom 64.3% had reduced kidney function. CKD was more common in women than in men ($p < 0.001$). Major etiologic factors included diabetes mellitus (29%), chronic glomerulonephritis (23%), chronic pyelonephritis (17%), and hypertension (10%). In multivariable analysis, diabetes, hypertension, dyslipidemia, obesity (BMI ≥ 30), and rural residence were independent predictors of CKD ($p < 0.05$).

Conclusion: CKD is highly prevalent among adults in the Kyrgyz Republic. Risk factors align with international data, but regional patterns show higher rates of chronic glomerulonephritis and pyelonephritis. Strengthening early detection, integrating CKD screening into national health programs, and focusing on high-risk groups—older adults, women, and rural populations—are crucial to reducing the CKD burden in Kyrgyzstan.

Keywords: Chronic Kidney Disease; Prevalence; Risk Factors; Diabetes; Hypertension; Dyslipidemia; Obesity; Kyrgyz Republic; Central Asia

Introduction

Chronic kidney disease (CKD), with a global prevalence of 13.4%, is one of the leading causes of morbidity and mortality related to noncommunicable diseases (1). It ranks 12th among the global causes of death and is projected to become the 5th leading cause of mortality by 2040 (2–4). CKD is an independent predictor of

premature death, increased hospitalization rates, economic burden for patients and healthcare systems, and reduced quality of life (5–9). In 2016, approximately 1.2 million deaths were attributed to CKD, and it is estimated that by 2040, CKD-related deaths will reach 2.2–4.0 million globally (10).

Between 1990 and 2016, the global burden of CKD showed a concerning upward trend: incidence increased by 89%, prevalence by 87%, mortality by 98%, and disability-adjusted life years by 62% (11). This rise is largely driven by the increasing prevalence of type 2 diabetes mellitus (T2DM), arterial hypertension (HTN), and obesity, alongside global population aging.

CKD is defined as the presence of structural or functional abnormalities of the kidneys persisting for more than three months and having clinical implications for health. The glomerular filtration rate (GFR) is considered the gold standard for assessing kidney function. A sustained decrease in GFR below 60 mL/min/1.73 m² for more than three months indicates CKD, whereas end-stage renal disease (ESRD) is de-

fined as a GFR below 15 mL/min/1.73 m². CKD is associated with an increased risk of developing cardiovascular disease (CVD) (8,9,12).

Asia has one of the highest prevalences of CKD globally and is currently experiencing a rapid rise in diabetes mellitus (DM) and arterial hypertension (HTN) (13). Most Central Asian countries are classified as low- and middle-income nations, characterized by constrained healthcare resources and the absence of comprehensive national CKD registries, resulting in insufficient data on the prevalence, burden, and impact of implemented health programs.

The objective of this study was to assess the prevalence of chronic kidney disease (CKD) in order to inform the development of national policies aimed at improving healthcare delivery for CKD patients.

Methods

A cross-sectional population-based study was conducted to evaluate the prevalence of CKD across all seven regions of the Kyrgyz Republic. A cluster sampling design was applied to ensure representativeness across different areas of the country. The sampling framework was based on territorial and demographic principles, taking into account urban and rural settings, sex, and age distribution.

A multistage cluster sampling method was used, involving the division of the country into administrative units - regions (oblasts), districts, rural municipalities, and settlements. At each stage, clusters were randomly selected to ensure representativeness of the sample.

Study participants included residents of all age groups from selected areas who had lived at their current address for at least 12 months. Pregnant women and individuals with cognitive impairments were excluded. The age structure of the sample was formed using stratified sampling, with an equal number of men and women included in each age stratum, ranging from 18–29 to 70–79 years.

The sample size included 10,478 adults, representing 94.8% of those invited to participate. Population data from the National Statistical Committee of the Kyrgyz Republic served as the basis for sample formation (<https://stat.gov.kg/ru/statistics/naselenie/>).

The study protocol was approved by the Ethics Committee of the National Center of Cardiology and Internal Medicine, and written informed consent was obtained from all participants.

After sample formation, the frequency of risk factors, disease severity, and etiologic causes of CKD were

assessed. The severity of CKD was determined according to staging based on kidney function and degree of microalbuminuria (MAU) (14).

Risk factors for end-stage kidney disease (ESKD) were defined according to the following parameters: blood glucose level, systolic blood pressure consistent with hypertension (≥ 140 mmHg), total cholesterol level, body mass index (BMI) indicative of obesity (≥ 25 kg/m²), as well as the presence of smoking habits and insufficient physical activity (< 30 minutes per day).

Each study participant underwent a standardized interview conducted by specially trained personnel, which included the collection of data on sociodemographic characteristics, behavioral and dietary habits, physical activity levels, and personal and family medical history. In addition, a physical examination was performed to assess anthropometric and physiological parameters, including height, body weight, waist circumference, blood pressure (BP), and heart rate.

Height and weight measurements were obtained according to a standardized protocol, and the body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). For blood pressure analysis, the mean value of the last two consecutive measurements was used. All participants also underwent fasting venous blood sampling and provided a morning urine sample for MAU testing.

Biochemical analyses included the determination of plasma glucose, lipid profile, uric acid, and serum creatinine levels. Urinary albumin concentration was assessed using a microalbuminuria test. The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the CKD-EPI equation (15).

The diagnosis of CKD was based on a single measurement of serum creatinine, eGFR, and MAU. Because of the cross-sectional design and reliance on a single assessment, transient reductions in kidney function or albuminuria could not be excluded, and CKD prevalence may therefore be over- or underestimated.

Newly diagnosed arterial hypertension was defined as a blood pressure $\geq 140/90$ mmHg recorded during the physical examination in individuals without a prior diagnosis of hypertension. Previously diagnosed hypertension was identified based on medical history confirming a documented diagnosis at primary healthcare facilities and/or the use of antihypertensive medications within the preceding two weeks. Blood pressure control among hypertensive participants was defined as achieving BP $< 140/90$ mmHg at the time of examination.

Newly diagnosed diabetes mellitus was identified in individuals without a prior diagnosis but who met the diagnostic criteria of the American Diabetes Association (ADA, 2010) (16). Dyslipidemia was defined as a total cholesterol level exceeding 5.2–6.2 mmol/L. Hyperuricemia was defined as a serum uric acid concentration > 420 $\mu\text{mol/L}$. Overweight and obesity were classified according to body mass index (BMI) values of 25.0–29.9 kg/m^2 and ≥ 30 kg/m^2 , respectively. Central obesity was defined as a waist circumference ≥ 90 cm in men and ≥ 85 cm in women.

To assess the prevalence of CKD in the general population, the minimum sample size was calculated using the Epi Info software, considering a 95% confidence level, a margin of error of $\pm 5\%$, and a design effect (DEFF) of 1.5. 95% confidence intervals (CIs) for prevalence estimates were computed using the Taylor series linearization method with finite population correction, implemented in the STATISTICA software, version 7.

Similarly, multivariable logistic regression models were constructed to identify factors associated with CKD, reduced kidney function, and albuminuria. The models included sociodemographic characteristics, behavioral and dietary habits, physical activity level, comorbid conditions, and laboratory parameters as independent variables.

In addition, the prevalence of arterial hypertension, diabetes mellitus, and dyslipidemia was estimated, and indicators of awareness, treatment, and control of these conditions among patients receiving therapy were determined.

Missing data were handled through listwise deletion (complete case analysis). Participants with missing values for any of the key variables included in the regression model were excluded from the multivariable analysis. The proportion of missing data for these variables was low ($< 3\%$) and was deemed unlikely to materially influence the findings.

Ethical Approval: Protocol № 4 of the meeting of the Ethics Committee, May 13, 2022.

Results

A total of 10,478 adult participants were enrolled in the study, with an overall response rate of 94.8%. All included participants had available data on estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR), forming the analytical sample for the present study.

The prevalence of CKD in the Kyrgyz Republic, defined as reduced kidney function (eGFR < 60

mL/min/1.73 m^2) and/or albuminuria (UACR ≥ 30 mg/g), was 10.8% (95% CI, 10.2–11.4). The prevalence of impaired kidney function and albuminuria alone was 3.6% (95% CI, 3.1–4.1) and 6.7% (95% CI, 6.4–7.1), respectively.

The distribution of CKD stages and albuminuria categories is presented in Table 1.

Table 1. Prevalence of chronic kidney disease in the Kyrgyz Republic.

Stage of CKD, % (95% CI)					Albuminuria, UACR		
C 1	C2	C3	C4	C5	A1	A2	A3
4.0 (3.6–4.4)	3.2 (2.9–3.5)	3.1 (2.8–3.4)	0.4 (0.28–0.52)	0.1 (0.04–0.16)	4.0 (3.6–4.4)	2.2 (1.9–2.5)	0.5 (0.37–0.63)
Total – 10.8%							

The overall prevalence of CKD was 10.8%, with stage 1 – 4.0%, stage 2 – 3.2%, stage 3 – 3.1%, stage 4 – 0.4%, and stage 5 – 0.1%.

The mean age of the study participants was 40.1 years, with 54.7% women and 45.3% men. Urban residents accounted for 52% of the study population, while 48% resided in rural areas.

A statistically significant difference was observed when comparing the prevalence of CKD stages and microalbuminuria (MAU) by sex. Women demonstrated poorer kidney function parameters, characterized by

lower estimated glomerular filtration rate (eGFR) and higher levels of albuminuria (Table 2).

Table 2. Prevalence of chronic kidney disease by sex.

Parameters	Quantity n (%)		
	Total	Males	Females
e-GFR, ml/min/1,73m ²			
≥90	7606 (72.6)	3399 (71.6)	4207 (73.4)
60-89	2495 (23.8)	1211 (25.5)	1284 (22.4)
30-59	329 (3.1)	123 (2.6)	206 (3.6)
15-29	39 (0.4)	10 (0.2)	29 (0.5)
<15	11 (0.1)	5 (0.1)	6 (0.1)
UACR, mg/g			
<30	9776 (93.3)	4520 (95.2)	5256 (91.7)
30-299	636 (6.1)	195 (4.1)	441 (7.7)
≥300	67 (0.6)	33 (0.7)	34 (0.6)

Abbreviations: e-GFR — estimated glomerular filtration rate; UACR — urine albumin-to-creatinine ratio. *P*<0.001

Specifically, the proportion of women with eGFR <60 mL/min/1.73 m² and microalbuminuria was significantly higher than that of men (*p*<0.001)

In addition, the prevalence of CKD – particularly at advanced stages – increased markedly with age in

our study population. Among participants aged 70 years and older, the prevalence of CKD reached 25.0%, with 64.3% of these individuals demonstrating impaired kidney function (Figure 1).

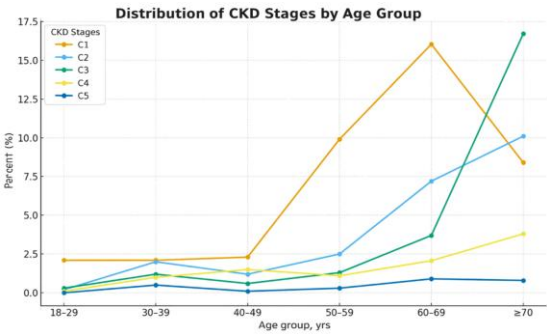


Figure 1. Distribution of chronic kidney disease by stages across different age groups.

Table 3. Prevalence of chronic kidney disease by stage across different age groups.

Age,yrs	CKD stage,%				
	C1	C2	C3	C4	C5
18-29	2.1 (1.8 – 2.3)	0.2 (0.1 – 0.2)	0.3 (0.2 – 0.4)	0,1 (0.04 – 0.6)	-
30-39	2.1 (1.8-2.3)	2.0 (1.7-2.2)	1.2 (0.9-1.4)	1,0 (0,8-1.1)	0.5 (0.3-0.6)
40-49	2.3 (2.0 – 2.5)	1.2 (0.9 – 1.4)	0.6 (0.4 – 0.7)	1,5 (1.2 – 1.7)	0,1 (0.04 – 0.1)
50-59	9.9 (9.39 – 10.4)	2.5 (2.2 – 2.7)	1.3 (1.07 – 1.5)	1,1 (0.9 – 1.3)	0.3 (0.2 – 0.4)
60-69	16.03 (15.36 – 16.7)	7,2 (6.75 – 7.65)	3.7 (3.36 – 4.04)	2,07 (1.80 – 2,3)	0,9 (0,7 – 1.09)
>70	8,4 (7.9 – 8.9)	10.1 (9.6 – 10.6)	16.7 (16.0 – 17.4)	3.8 (3.45 – 4.15)	0.8 (0.62 – 0.98)

The prevalence of CKD by stage in the cities of Bishkek and across different regions of the Kyrgyz Republic is presented in Figure 2.

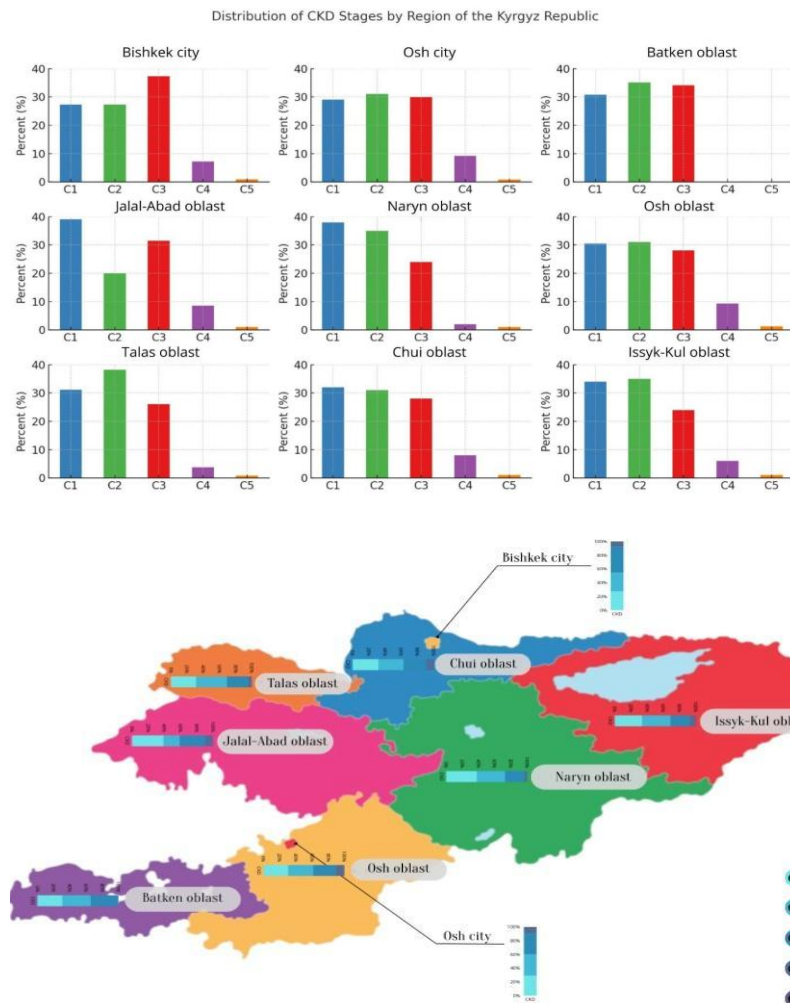


Figure 2. The prevalence of CKD by stage in the cities of Bishkek and across different regions of the Kyrgyz Republic.

Table 4. Prevalence of chronic kidney disease in the Bishkek and Osh cities and across the regions of the Kyrgyz Republic.

Region	CKD stages				
	C1	C2	C3	C4	C5
Bishkek city	306	305	418	81	10
Osh city	328	351	339	104	9
Batken oblast	317	362	351	0	0
Jalalabad oblast	441	226	356	96	11
Naryn oblast	430	396	271	23	11
Osh oblast	345	351	317	105	14
Talas oblast	351	430	294	43	9
Chui oblast	362	351	317	90	11
Issyk-Kul oblast	385	396	271	68	11

Among the surveyed participants, CKD stages 1–2 were identified in 2,495 individuals. Stage C3 CKD was diagnosed in 329 participants, stage C4 in 39, and stage C5 in 11 participants.

CKD risk factors were highly prevalent among the adult population: obesity was observed in 29.9%,

hypertension in 28.2%, diabetes mellitus in 20.6%, and dyslipidemia in 36.4% of participants. Smoking was significantly more common among men (54.6%) compared to women (3.4%) (Table 5).

Table 5. Risk factors for chronic kidney disease in the study population.

Risk factors	Quantity n (%)		
	Total	Males	Females
Smoking			
Never	7215 (68.8)	1718 (36.2)	5497 (95.9)
Former	477 (4.6)	437 (9.2)	40 (0.7)
Current	2787 (26.6)	2592 (54.6)	195 (3.4)
Physical inactivity (<150 min/week)	3472 (33.1)	1724 (36.3)	1748 (30.5)
BMI ≥25,0	2231 (21.3)	1156 (24.3)	1075 (18.7)
BMI ≥30,0	902 (8.6)	455 (9.6)	447 (7.8)
Arterial hypertension			
None	5529 (52.8)	2339 (49.3)	3190 (55.7)
Newly detected	1658 (15.8)	883 (18.6)	775 (13.5)
Previously diagnosed	3290 (31.4)	1525 (32.1)	1765 (30.8)
Diabetes mellitus			
None	8318 (79.4)	3808 (80.2)	4510 (78.7)
Newly diagnosed	776 (7.4)	404 (8.5)	372 (6.5)
Previously diagnosed	1383 (13.2)	535 (11.3)	848 (14.8)
Blood pressure			
<140 mmHg	2398 (81.2)	1102 (81.2)	1296 (81.1)
140-199 mmHg	416 (14.1)	179 (13.2)	237 (14.8)
≥200 mmHg	142 (4.8)	76 (5.6)	66 (4.1)
Dyslipidemia	3823 (36.4)	2098 (44.2)	1725 (30.1)
Hyperuricemia	1332 (12.7)	1120 (23.6)	212 (3.7)
Previously diagnosed kidney disease	484 (4.6)	227 (4.8)	257 (4.5)
Previously diagnosed cardiovascular disease	417 (3.9)	194 (4.1)	223 (3.9)
Place of residence			
Urban	5487 (52.4)	2460 (51.8)	3027 (52.8)
Rural	4991 (47.6)	2287 (48.2)	2704 (47.2)
Education level			
Secondary education	3484 (33.2)	1431 (30.1)	2053 (35.8)
Vocational secondary education	3414 (32.6)	1604 (33.8)	1810 (31.6)
Higher education	3580 (34.2)	1713 (36.1)	1867 (32.6)

Thus, analysis of CKD risk factors revealed that a higher prevalence of CKD was observed among older individuals, women, rural residents, and participants with lower levels of education and income. Increased

CKD prevalence was also noted among former smokers, physically inactive individuals, and those with es-

tablished risk factors such as obesity, hypertension, diabetes mellitus, dyslipidemia, and cardiovascular disease.

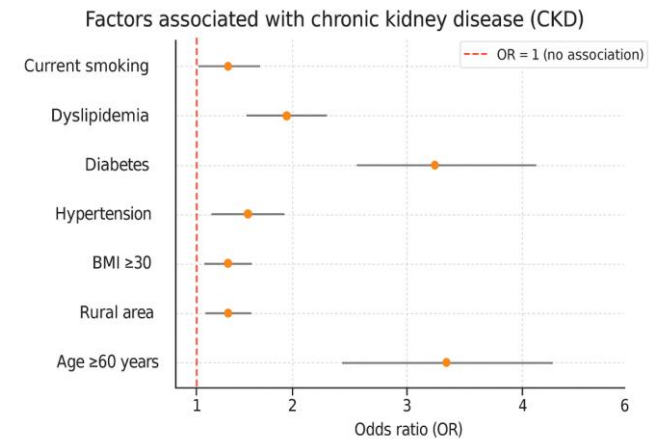


Figure 3. Factors associated with chronic kidney disease.

Table 6. Determinants of chronic kidney disease.

Factor	Odds ratio (95% CI)	P
Age ≥60 years	4.8 (3.5–6.4)	<0.001*
Male	1.2 (0.9–1.5)	0.21
Living in a rural area	1.4 (1.1–1.8)	0.012*
BMI ≥ 30	1.3 (1.0–1.7)	0.047*
Arterial hipertension	2.6 (1.9–3.4)	<0.001*
Diabetes mellitus	3.9 (2.8–5.4)	<0.001*
Dyslipidemia	1.5 (1.1–2.0)	0.02*
Current smoking	1.1 (0.8–1.5)	0.36

(*) P<0.05

In multivariable logistic regression analysis, age over 60 years, diabetes mellitus, hypertension, dyslipidemia, rural residence, and a BMI ≥30 were identified as independent predictors of CKD ($p<0.05$) (Figure 3).

The etiological structure of CKD is shown in Figure 4.

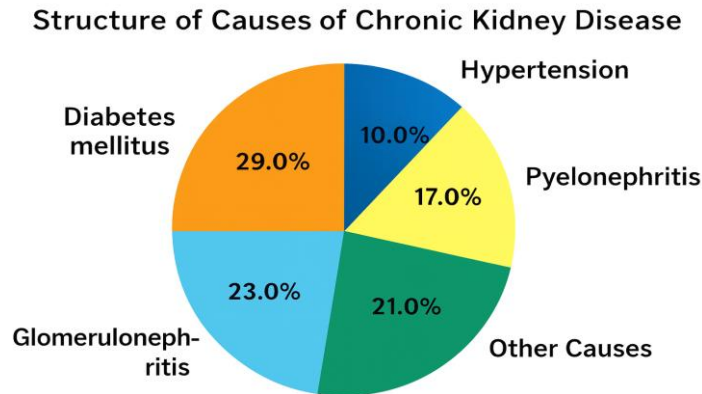


Figure 4. Etiological structure of chronic kidney disease in the Kyrgyz Republic.

Analysis of the etiological structure of CKD in our cohort revealed that the most common causes were diabetes mellitus (29%), chronic glomerulonephritis

(23%), chronic pyelonephritis (17%), arterial hypertension (10%), and other causes (21%).

Discussion

According to the results of a systematic review and meta-analysis of observational studies that included 100 studies with a total of 6,908,440 participants, the average global prevalence of chronic kidney disease (CKD) in the general population was estimated at 13.4% (95% CI: 11.7–15.1%), while the prevalence of stages 3–5 CKD was 10.6% (95% CI: 9.2–12.2%) (16). The stage-specific prevalence was as follows: stage 1 – 3.5% (2.8–4.2%), stage 2 – 3.9% (2.7–5.3%), stage 3 – 7.6% (6.4–8.9%), stage 4 – 0.4% (0.3–0.5%), and stage 5 – 0.1% (0.1–0.1%). These rates varied across regions, ranging from 7% in South Asia and 8% in Africa to 11% in the United States and 12% in Europe and South America (16).

The overall CKD prevalence in Central Asia remains uncertain; however, based on data from neighboring countries and global estimates, CKD represents a significant public health concern. According to the Global Burden of Disease Study (2021), the age-standardized prevalence rate of CKD in the Central Asia region was approximately 10,698 per 100,000 population, equivalent to about 10.7% (95% UI: 10,022.94–11,348.10) (17). It should be noted that a limitation of this estimation method is the inclusion of only individuals with estimated glomerular filtration rate (e-GFR) <60 mL/min/1.73 m², which does not account for patients with early-stage CKD (stages 1–2). Therefore, the true prevalence of CKD in Central Asia, including early stages, is likely somewhat higher.

In our study, the overall prevalence of CKD was 10.8%, with stage 1 – 4.0%, stage 2 – 3.2%, stage 3 – 3.1%, stage 4 – 0.4%, and stage 5 – 0.1%. Patients receiving renal replacement therapy were not included in our study, which, although to a minor extent, may have influenced the overall CKD prevalence estimate in the Kyrgyz Republic.

Comparable data from neighboring Central Asian countries are limited but suggest a similar or slightly higher burden. In Kazakhstan, a nationally representative survey of 6,720 adults aged 18–69 years across 14 regions and three major cities reported that mild CKD was most frequently detected in East Kazakhstan (10.4%), followed by Almaty and Karaganda regions (7.8–8.0%). CKD with eGFR < 60 mL/min/1.73 m² was most prevalent in East Kazakhstan (15.3%), followed by Almaty (10.6%) and Atyrau (9.4%) (2). In Uzbekistan, approximately 118,026 CKD patients were registered

nationally in 2020, although the lack of population denominator precludes precise prevalence estimates (18).

Overall, these findings indicate that the CKD prevalence in the Kyrgyz Republic is broadly consistent with regional trends, while differences in study design, diagnostic criteria, and registration systems likely contribute to variability between countries.

Global epidemiological data indicate that CKD exhibits significant differences by sex, with variations observed in both disease progression and outcomes between men and women. Meta-analyses indicate that women have a slightly higher prevalence of CKD compared to men (13.0% vs. 12.1%, respectively), which may be attributed to longer life expectancy, more frequent healthcare utilization, and earlier detection of mild disease. However, men tend to experience more rapid CKD progression and higher mortality from renal complications (19).

The results of our study demonstrate a similar trend: women exhibited a higher prevalence of reduced eGFR and albuminuria compared to men, confirming the greater burden of CKD among females. Specifically, the proportion of women with eGFR <60 mL/min/1.73 m² and microalbuminuria was significantly higher than that of men.

Thus, our findings are consistent with global observations indicating that CKD is more prevalent among women, although men are more likely to develop severe outcomes and end-stage kidney disease (20, 21–23).

In our study, the prevalence of CKD - especially in its advanced stages - rose substantially with increasing age. Among participants aged 70 years and older, 25.0% had CKD, and 64.3% of them exhibited impaired kidney function.

These results are consistent with the well-established pattern reported in previous studies, showing that the prevalence of CKD increases sharply with advancing age. According to CDC/NIDDK data from the United States, CKD is most common among individuals aged ≥65 years (approximately 34%), while in several European cohorts, the proportion of individuals with CKD stages 3–5 reaches approximately 25–33% in those aged 70–79 years and exceeds 50% among those aged 80 years and older; some reviews even report prevalence rates exceeding 40% in individuals over 65 years of age (24, 25).

The differences between our findings (25.0% in participants aged ≥ 70 years) and the higher values reported in some international studies likely reflect methodological and population-related factors - such as differences in CKD definitions (inclusion or exclusion of albuminuria), sample age structure, prevalence of comorbid conditions (diabetes, hypertension), access to healthcare, and study design. Additionally, regional variations and limitations in diagnostic accessibility may lead to underdiagnosis of early CKD stages in certain settings.

Taken together, our findings confirm the general global trend of a significant increase in CKD burden with age, while providing slightly lower prevalence estimates among older adults compared to some large Western cohorts.

Among the surveyed participants, CKD stages C1–C2 were detected in 2,495 individuals, while 329 participants had stage C3, 39 had stage C4, and 11 were diagnosed with stage G5 CKD. A lower number of patients with stages C4 and C5 CKD was observed in the Talas and Batken regions, which can be attributed to the limited availability of nephrologists and hemodialysis centers in these remote areas, leading to patient migration to larger cities and other regions.

Analysis of CKD risk factors demonstrated a higher prevalence among older individuals, females, rural residents, and participants with lower educational attainment. CKD prevalence was also elevated among former smokers, individuals with low physical activity, and those with established comorbidities, including obesity, hypertension, diabetes mellitus, dyslipidemia, and cardiovascular disease. In multivariable analysis, age over 60 years, diabetes mellitus, hypertension, dyslipidemia, rural residence, and a BMI ≥ 30 were identified as independent predictors of CKD.

The results of our study are consistent with findings from previous international studies. Diabetes mellitus and arterial hypertension are recognized as leading causes and key risk factors for the development and progression of CKD in most population-based studies (1,24,25).

In addition, obesity is considered an independent predictor of CKD. Meta-analyses have shown that individuals with an elevated BMI have approximately a 1.8-fold higher risk of developing CKD, with a clear dose-response relationship between the degree of obesity and the decline in kidney function (26).

In our study, we found that dyslipidemia was associated with an increased risk of CKD development and progression. An unfavorable lipid profile - marked by elevated triglycerides and low HDL cholesterol - was

linked to a more rapid decline in glomerular filtration rate (27).

It is also noteworthy that the association identified in our study between rural residence and higher CKD prevalence aligns with previously published data. Several studies have reported that CKD tends to be more common and more severe in rural areas. This pattern has been attributed to limited access to healthcare services, higher exposure to occupational and environmental hazards, and lower public awareness of chronic noncommunicable diseases (28, 29).

According to recent Global Burden of Disease data, diabetic nephropathy and hypertensive nephropathy account for the majority of CKD burden worldwide, while glomerulonephritis remains an important cause, especially in low- and middle-SDI regions. In this context, our cohort shows a relatively higher share of chronic glomerulonephritis and chronic pyelonephritis which may be explained by regional epidemiologic patterns and differences in the provision of medical care and diagnostic methods. In other countries, the etiological distribution of CKD also varies. For example, studies from Saudi Arabia indicate that diabetic nephropathy is the predominant cause of CKD in that setting, highlighting the influence of regional epidemiological and healthcare characteristics (30).

Although our survey represents a population-based screening of CKD, arterial hypertension accounted for only the third most common cause of CKD in our dataset. This finding contrasts with global data, where hypertension is recognized as one of the leading etiologies of CKD. The lower proportion observed in our study is likely explained by systemic underdiagnosis and underreporting of hypertension in the Kyrgyz Republic. According to the KIOD-2007 survey, only 27% of individuals with elevated blood pressure were aware of their condition, and national electronic health record data show a much lower “observed” prevalence of hypertension compared with population-based surveys such as WHO STEPS and INTEREPID (31–34). These discrepancies highlight substantial gaps in blood pressure screening, registration, and etiological attribution within the healthcare system, resulting in the underestimation of hypertensive nephropathy in national CKD statistics.

In contrast, our cohort demonstrated a relatively higher prevalence of chronic pyelonephritis (17%), which likely reflects regional characteristics - specifically, the high burden of urinary tract infections and the

limited availability of early diagnostic services for metabolic disorders. The relatively low proportion of hypertensive nephropathy (10%) may be explained by potential underrecognition of patients with long-standing hypertension without overt proteinuria, as well as by differences in the classification of CKD etiologies at the regional level.

An analysis of CKD prevalence according to altitude of residence was not conducted in the present study. The sampling framework was designed to ensure representativeness of the adult population of the Kyrgyz Republic, encompassing households located in both highland and lowland regions. However, the distribution of participants across altitude categories was uneven, which could have reduced the statistical robustness of altitude-specific comparisons. As the primary aim of the study was to estimate the overall population-based prevalence of CKD, the analysis was performed for the total representative sample without stratification by altitude.

Conclusion

In this population-based study, the prevalence of CKD among the adult population of the Kyrgyz Republic was 10.8%, which is comparable to global estimates. Over the past decade, there has been a growing trend in CKD prevalence, likely attributable to the increasing burden of diabetes mellitus, hypertension, and obesity, as well as improvements in laboratory diagnostic capacity and the implementation of screening programs.

Diabetes mellitus, chronic glomerulonephritis, and chronic pyelonephritis were the predominant causes of CKD in this cohort, reflecting regional characteristics of disease pathogenesis and underlying socioeconomic factors.

Author Contributions: A.D. and B.A. - the overall conceptualization of the study and the development of its methodological framework, drafted the initial version of the manuscript, coordinated the integration of contributions from all co-authors. K.A., O.T., T.S., K.S., and K.Y. contributed to data acquisition, validation, and comprehensive statistical analysis, supporting the interpretation of findings across regional contexts. K.R. provided senior academic supervision and oversight throughout all stages of the research process, offering

This study has several limitations. First, the classification of CKD status was based on a single measurement of e-GFR and urinary albumin concentration. This approach may lead to an overestimation of CKD prevalence, as the diagnosis requires confirmation of persistent abnormalities over at least three months. Repeated assessment of renal biomarkers over time would provide more accurate estimates of disease prevalence.

Second, only adult participants were included in the study, which limits the generalizability of the findings to the pediatric population.

Third, the study did not include data on patients receiving renal replacement therapy, which may have resulted in a slight underestimation of CKD stage 5 cases. According to national data, as of September 2025, the prevalence of dialysis therapy in the Kyrgyz Republic was approximately 65 patients per 100,000 population (0.065%), which likely has minimal impact on the overall population-based CKD prevalence estimate.

Finally, due to the cross-sectional nature of the study, causal relationships between CKD and associated risk factors cannot be established.

Despite improvements in detection, population-level control of CKD and its major risk factors remains insufficient. To reduce the burden of CKD in the Kyrgyz Republic, a comprehensive strategy is needed - one that includes expanding early detection programs, integrating CKD surveillance into national noncommunicable disease monitoring systems, improving awareness among the general population and primary care providers, and implementing cross-sectoral interventions aimed at preventing diabetes, hypertension, and obesity. Particular attention should be directed toward vulnerable groups, including older adults, women, and residents of rural areas.

methodological guidance, ensuring adherence to scientific and ethical standards. All authors contributed to the interpretation of the data, participated in the critical revision of the manuscript for important intellectual content, and approved the final version for publication.

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Experience of Using Sacubitril/Valsartan in an Asian Patient with Comorbidities: Chronic Heart Failure, Atrial Fibrillation, and Chronic Kidney Disease

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A 68-year-old Asian man was admitted with decompensated chronic heart failure with a left ventricular ejection fraction of 20%, permanent arterial fibrillation, and chronic kidney disease. Sacubitril/Valsartan (Uperio) was prescribed.

This review details the initiation of sacubitril/valsartan in an Asian patient with heart failure with low ejection fraction (20%) and comorbidities. The paper highlights the pharmacodynamic and pharmacokinetic profiles of Sacubitril/Valsartan. The focus is on a thorough review of clinical trials to assess the therapeutic efficacy and potential adverse events associated with Sacubitril/Valsartan administration in this specific patient group.

Since 2014, sacubitril/valsartan has been widely prescribed for heart failure. Nevertheless, the coexistence of additional diseases such as arthritis, renal insufficiency, diabetes mellitus, or chronic lung disease with the heart failure syndrome should logically require a modification of treatment, outcome assessment, or follow-up care.

Keywords: Sacubitril/Valsartan; Neprilysin; Chronic Heart Failure; Arterial Fibrillation; Chronic Kidney Disease

Introduction

Sacubitril/valsartan is a neprilysin inhibitor and angiotensin II receptor antagonist widely used in the treatment of chronic heart failure (CHF) with reduced ejection fraction (HFrEF) (1). It was approved in 2015 by the US Food and Drug Administration (FDA) to reduce the risk for cardiovascular (CV) death and hospitalization in patients with CHF (2,3). The therapeutic action of the combined agent is initiated by sacubitril, an inactive prodrug that requires in vivo esterase cleavage to yield the active metabolite, sacubitrilat. Sacubitrilat's mechanism is predicated on neprilysin inhibition, preventing the breakdown of natriuretic and other vasoactive peptides. The resulting increase in natriuretic peptide concentration induces beneficial hemodynamic and renal effects, notably systemic vasodilation and increased sodium excretion, leading to ECF volume reduction. The dual component, valsartan, acts independently as an angiotensin II type 1 receptor blocker

(ARB) to oppose the biological consequences of angiotensin II signaling (4). Since the landmark PARADIGM-HF trial in 2014, sacubitril/valsartan (LCZ696, Entresto®) has been widely adopted and is now a recommended standard of care for the treatment of heart failure (HF), including in the elderly population (5,6). However, in patients with comorbid conditions such as atrial fibrillation (AF) and chronic kidney disease (CKD), therapy requires a special approach, considering potential risks and individual patient characteristics.

CHF represents a heterogeneous and complex clinical syndrome defined by underlying structural or functional abnormalities that compromise the heart's ability to fill or eject blood adequately. The primary clinical features of HF are dyspnea and fatigue, typically resulting in limited physical capacity (exercise intolerance), alongside fluid retention that commonly presents as peripheral edema or pulmonary and/or

splanchnic venous congestion. Clinical presentation is highly variable, a subset of patients may predominantly experience exercise limitation with scant evidence of fluid accumulation, while others report a greater focus on symptoms such as edema, dyspnea, or chronic fatigue (7). The defining criteria for heart failure with reduced ejection fraction (HFrEF) have evolved, with different established guidelines proposing left ventricular ejection fraction (LVEF) thresholds of $\leq 35\%$, $< 40\%$, and $\leq 40\%$ (8-10).

The prevalence of HF is increasing as the population ages (11). Each hospitalization event is associated with worsening long-term prognosis. Approximately one in four patients is readmitted for HF, and 10 percent may die within 30 days of discharge (12,13). Although survival has improved, the absolute mortality rates for HF remain approximately 50% within 5 years of diagnosis (14,15). In the ARIC study, the 30-day, 1-year, and 5-year case fatality rates after hospitalization for HF were 10.4%, 22%, and 42.3%, respectively (16).

In the Republic of Kazakhstan, mortality from cardiovascular disease decreased from 160.4 cases per 100 thousand population in 2019 to 128.9 cases per 100 thousand population in 2022. The incidence of HF also decreased, from 601.2 cases per 100 thousand population in 2019 to 585.1 cases per 100 thousand population in 2022 (17).

The ACCF/AHA staging criteria for heart failure (HF) incorporate both cardiac structural changes and underlying risk factors as determinants of the condition. Relative to the general population, patients diagnosed with HF demonstrate an increased susceptibility to developing atrial fibrillation (AF) (18). Furthermore, a pronounced relationship exists between the severity of HF, as defined by the NYHA functional class, and the prevalence of AF; this prevalence escalates markedly from 4% in NYHA class I patients to 40% in those categorized as NYHA class IV (19). AF is also a strong independent risk factor for the subsequent development of HF (20). Atrial fibrillation (AF) is recognized as the most clinically significant arrhythmia encountered in routine

practice. Its prevalence is estimated at 1–3% in the general population, yet it increases sharply with advancing age, reaching up to 9% in individuals ≥ 65 years old and up to 17% in those ≥ 80 years old (20, 21). Furthermore, heart failure (HF) represents the primary cause of mortality and is a major contributor to hospitalizations among patients with AF (22).

Another risk factor for developing HF is chronic kidney disease. The global prevalence of Chronic Kidney Disease (CKD) has seen a marked increase, impacting an estimated 843.6 million individuals globally in 2017 (23). Despite advancements leading to a reduction in mortality among patients with End-Stage Kidney Disease (ESKD) (24), comprehensive analyses from the Global Burden of Disease (GBD) studies indicate that CKD has concurrently risen to prominence as a major worldwide cause of death (25).

The FortiHFy clinical development program represents the largest worldwide effort in the heart failure field, comprising over 40 studies. It includes pivotal trials across the entire spectrum of heart failure, such as PARADIGM-HF, PIONEER-HF, TRANSITION, PROVE-HF, PARAGON-HF, and PARAMOUNT. To date, more than 30,000 patients globally have participated in the clinical trials of Entresto, which is currently prescribed to an estimated 2.8 million patients worldwide (26). Data from these trials demonstrate that sacubitril/valsartan therapy significantly reduces the risk of cardiovascular (CV) death or HF hospitalization by 20% (relative reduction), and all-cause mortality by 16% (relative reduction) (27).

Safety data on important safety topics of interest, such as hypotension, hyperkalemia, renal impairment, angioedema, and hepatotoxicity, were consistent with extensive prior experience in adults. Adverse effects observed very commonly ($\geq 10\%$) with sacubitril/valsartan administration are hypotension (systolic blood pressure ≤ 95 mmHg or symptomatic), hyperkalemia, and renal impairment.

Case Presentation

A 68-year-old asian man was admitted with decompensated CHF (left ventricular ejection fraction of 20%), permanent AF, and CKD (eGFR – 38 mL/min/1.73 m²). Before admission, the patient was maintained on standard medical therapy, which encompassed a β -blocker, a mineralocorticoid receptor antagonist, an angiotensin-converting enzyme inhibitor (ACEI), diuretics, and an anticoagulant (dabigatran). Hospitalization frequency was two times in one month, and symptoms

such as dyspnea, fatigue, and recurrent hospitalizations for CHF persisted.

Medical history: The patient has been under the observation of a general practitioner since 2014, with the following diagnoses: Coronary artery disease. Effort angina, functional class III. Myocardial infarction in 2014. Arterial hypertension grade 3, stage 3. Since 2018, the patient has been monitored by a nephrologist, phar-

macological treatment was not consistently administered, management relied on diet adherence. The first episodes of shortness of breath during physical exertion, discomfort in the heart, and severe fatigue appeared 4-5 years ago. Over the past year, a gradual deterioration in the tolerance of physical activity has been noted. Anthropometrics: Height: 165 cm, weight: 70 kg. Laboratory tests on admission day: WBC $8.4 \times 10^9/L$, RBC $4.5 \times 10^{12}/L$, Hemoglobin 146g/L, Platelets $336 \times 10^9/L$, ESR 29mm/h. Biochemistry: Total protein 69g/L, Urea 8.7mmol/L, Creatinine $125 \mu\text{mol}/L$, Glucose 5.6mmol/L, Magnesium 1.1mmol/L, ALT 35U/L, AST 25U/L, Total bilirubin $\sim 7.4 \mu\text{mol}/L$, High-sensitivity CRP 7.1mg/L, Creatinine clearance $38 \text{ mL}/\text{min}/1.73 \text{ m}^2$. Urinalysis: urine volume 40mL, Density 1.012, Protein 0.30g/L, Glucose negative, Bilirubin negative, pH 5.00, Ketones 2.00mmol/L, Leukocytes 10–15. Electrolytes: Ionized calcium 1.18mmol/L, Potassium 4.8mmol/L, Sodium 133mmol/L. Lipid profile: Total cholesterol 8.6mmol/L, HDL 1.05mmol/L, LDL 6.89mmol/L, Triglycerides 2.1mmol/L, Atherogenic coefficient 7.1, Cardiovascular risk index 6.5. Cardiac Markers: Troponin I 0.028ng/mL, ProBNP – 4500ng/mL.

Instrumental examinations. ECG from May 2025: Atrial fibrillation with a heart rate of 92 beats per minute. Incomplete right bundle branch block.

Cardiac ultrasound from May 2025 (before treatment): Aortic valve - tricuspid, cusps thickened, open-

ing not restricted. Mitral valve: cusps thickened, movements asynchronous. Tricuspid valve and pulmonary valve cusps are unchanged. Interatrial and interventricular septa intact. Heart chambers dilated. Global and regional myocardial contractility was significantly reduced. Pericardium without abnormalities. The inferior vena cava (I) – dilated, collapses on inspiration less than 50%. Heart chambers: dilated. Diffuse hypokinesia of the left ventricle (LV) walls. Global systolic function of the left ventricle – EF 20%. Tricuspid regurgitation grade 2, mitral regurgitation grade 1. Moderate pulmonary hypertension. Right ventricular systolic pressure (RVSP) – 60 mmHg. Diastolic dysfunction of the left ventricle, type I.

Laboratory tests (10th day of hospitalization): Total cholesterol 3.9mmol/L, Troponin I up to 0.04 ng/mL, ProBNP before treatment – decreased to 2700ng/mL. Urea 7.7mmol/L, Creatinine $121 \mu\text{mol}/L$. Urinalysis: Density 1.015, Protein 0.20g/L, Ketones 1.08mmol/L, Leukocytes 7-10.

Cardiac ultrasound on the 10th day of hospitalization: The study was conducted against the background of atrial fibrillation. Dilation of both atria is observed, with a decrease in dynamics. Diffuse hypokinesia of all walls of the LV and RV. The global systolic function of the left ventricle and EF is significantly reduced to 36%, with improvement in dynamics. Mitral and tricuspid valve insufficiency of grade 1. Diastolic dysfunction of the left ventricle of type 1 (Figure 1).

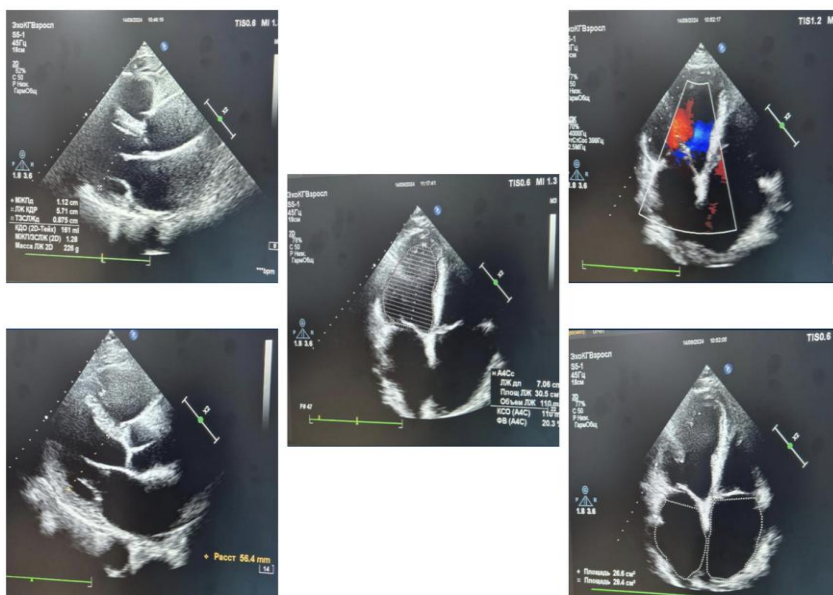


Figure 1. Cardiac ultrasound on the 10th day of hospitalization. The study was conducted against the backgrounds of atrial fibrillation. Dilation of both atria is observed, with a decrease in dynamics. Diffuse hypokinesia of all walls of the LV and RV. The global systolic function of the left ventricle and EF is significantly reduced to 36%, with improvement in dynamics. Mitral and tricuspid valve insufficiency of grade 1. Diastolic dysfunction of the left ventricle of type 1.

Coronary Angiography from May 2025: Left type of blood supply. LEFT MAIN: Patent, no abnormalities. PDA: Tandem stenosis of the distal third up to 70%,

blood flow velocity (TIMI III). OM: Patent, no abnormalities, blood flow velocity (TIMI III). RCA: Patent, no abnormalities, blood flow velocity (TIMI III) (Figure 2).

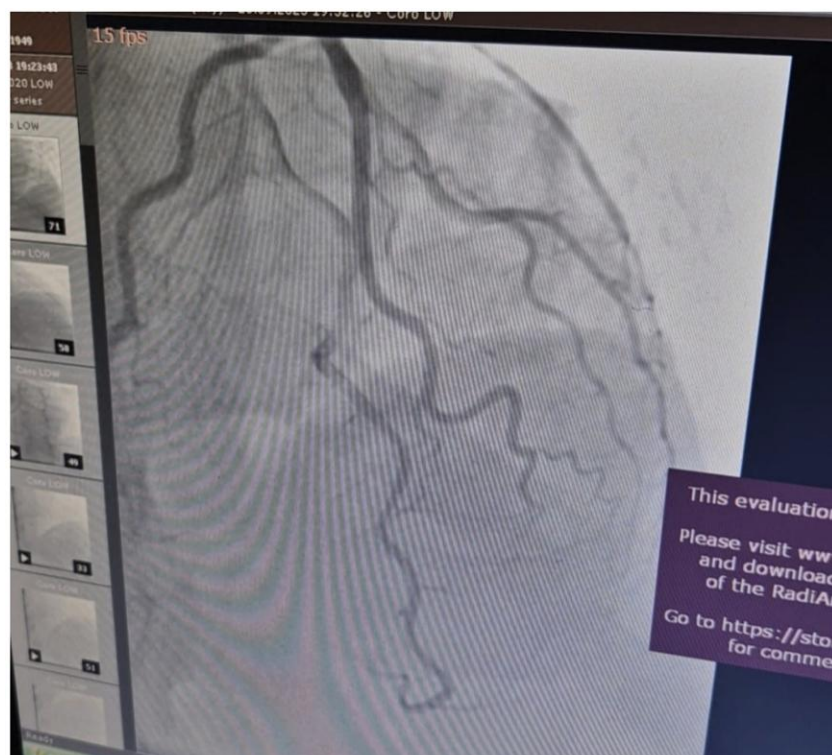


Figure 2. Coronary Angiography from May, 2025: Left type of blood supply. LEFT MAIN: Patent, no abnormalities. PDA: Tandem stenosis of the distal third up to 70%, blood flow velocity (TIMI III). OM: Patent, no abnormalities, blood flow velocity (TIMI III). RCA: Patent, no abnormalities, blood flow velocity (TIMI III).

A clinical diagnosis was made: Coronary artery disease. Effort angina pectoris, functional class III. Myocardial revascularization by stenting of the left anterior descending artery (LAD). History of myocardial infarction (2014). Chronic heart failure, NYHA functional class II, stage IIA. Arterial hypertension, grade 3, stage 3, very high cardiovascular risk (SCORE 20%). Chronic kidney disease, stage 3B (eGFR 38ml/min/1.73m²). Permanent atrial fibrillation. CHA2DS2-VASC score: 6. HAS-BLED score: 3.

Treatment plan: Atorvastatin 20mg – once daily after meals in the evening, Dabigatran 110mg – 1 tablet 2 times daily (morning and evening), Carvedilol 6.25mg

– ½ tablet twice daily (morning and evening), Verospiron 100mg – 1 capsule once daily in the morning, Trigrim 5mg – 1 capsule once daily in the morning, then increase to 10mg once daily, Dapagliflozin 10mg – 1 tablet once daily after meals.

Introduction of Sacubitril/valsartan into the therapeutic strategy. The ACE inhibitor (Perindopril 5mg) was discontinued, and after a 36-hour washout period, the patient started Uperio at a dose of 50mg (24/26mg) twice daily. On the 3rd day of hospitalization, the dose was increased to 100mg twice daily. Blood pressure and potassium levels were monitored at the first and second weeks (within normal limits).

Discussion

Patient's general condition improved, symptoms such as dyspnea, fatigue declined on the 10th day of hospitalization. The patient continues to take Uperio at a dose of 100mg twice daily. After three months of therapy, there was a reduction in hospitalization frequency (one in three months), improvement in dyspnea (NYHA II), and increased exercise tolerance.

Cardiac ultrasound from August 2025 (after three months of discharge). Dilation of both atria is observed, with a decrease in dynamics. Diffuse hypokinesia of all walls of the LV and RV. The global systolic function of the left ventricle and EF is significantly reduced to 38%, with improvement in dynamics. Mitral and tricuspid valve insufficiency of grade 1. Diastolic dysfunction of the left ventricle of type 1 (Figure 3).

The ejection fraction improved from 20% to 36% (on the 10th day of hospitalization), to 38% (after three months). NT-proBNP levels decreased by 60% on the 10th day of hospitalization (from 4500 ng/mL to 2700 ng/mL), and after three months, decreased from 2700

ng/mL to 560 ng/mL. Blood pressure stabilised at 110/70 mmHg. Renal function remained stable (eGFR at 36 mL/min/1.73 m², potassium – 4.8 mmol/L, Urea 7.2 mmol/L, Creatinine 119 µmol/L).

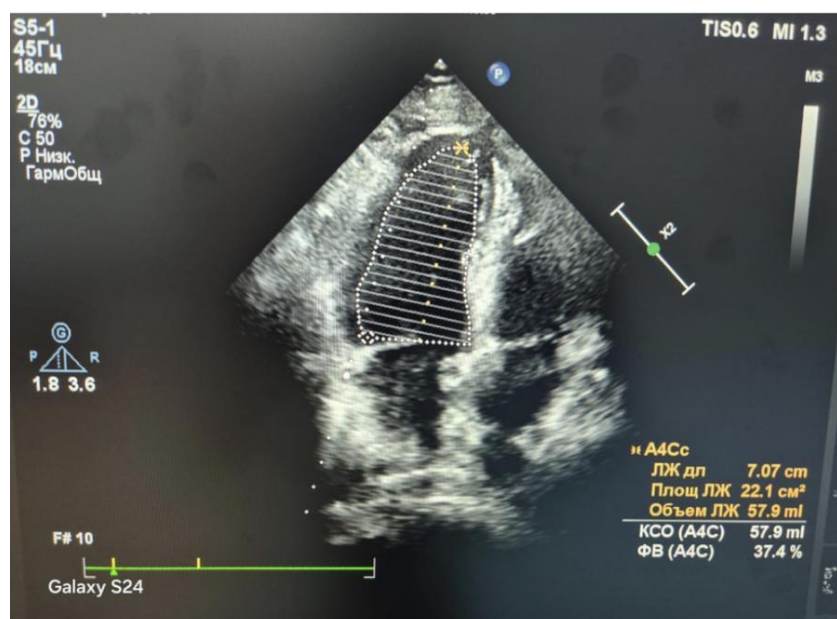


Figure 3. Cardiac ultrasound after three month of discharge. Dilation of both atria is observed, with a decrease in dynamics. Diffuse hypokinesia of all walls of the LV and RV. The global systolic function of the left ventricle and EF is significantly reduced to 38%, with improvement in dynamics. Mitral and tricuspid valve insufficiency of grade 1. Diastolic dysfunction of the left ventricle of type 1.

Clinical efficacy and good tolerability of sacubitril/valsartan were demonstrated in an Asian patient with concomitant CHF, AF, and CKD. Successful management necessitated meticulous dose titration and rigorous monitoring of blood pressure, potassium homeostasis, and kidney function.

In Study B2314, the incidence of renal impairment adverse events/serious adverse events (AEs/SAEs) was consistently lower with sacubitril/valsartan vs enalapril in adults with HFrEF. Also, the percentages of adults with categorical eGFR decreases, and notably abnormal serum creatinine elevations were lower in the sacubitril/valsartan group compared with the enalapril group. The proportion of reported deaths is relatively low,

with fewer deaths in the sacubitril/valsartan group (4.3% (n=8)) compared with the enalapril group (6.4% (n=12)), which is reassuring (26). During the administration of the drug, our patient had an improvement in the ejection fraction, and no deterioration was observed in the kidneys. The indicators of laboratory tests of kidney function were within normal limits on the 10th day of hospitalization and three months after discharge. Comparatively, previously, the patient had frequent hospitalizations (up to 2 times a month) while taking an angiotensin-converting enzyme inhibitor, persistent complaints of shortness of breath, and edema on the lower extremities.

Conclusion

Data regarding the effectiveness of medical therapy for patients with advanced HFrEF is limited, and survival without heart transplantation or Left Ventricular Assist Device (LVAD) therapy remains exceedingly poor (28). Despite established clinical advantages of sacubitril/valsartan in HFrEF patients with mild-to-moderate symptomatology, robust evidence regarding its safety profile, efficacy, and tolerability in individuals

with advanced heart failure is currently restricted. Following the initiation of the therapy, a reduction in the patient's hospitalization frequency was observed; notably, no hospital admissions occurred during the entire observation period.

Ongoing research and clinical trials will further elucidate the benefits and safety profiles of this innovative treatment in diverse populations. In conclusion,

Sacubitril/Valsartan represents a vital advancement in heart failure management. Its application in patients with complex medical histories requires careful monitoring and management strategies to maximize its benefits while minimizing risks.

Patient consent

Patient was examined and treated at the «Almaty Sema clinic» in May 2025. The diagnostic search included clinical examination, laboratory tests, and instrumental methods, such as cardiac ultrasound and selective coronary angiography. The treatment program included: drug correction of CHF. Status dynamics were monitored during the hospitalization period and three months after discharge. The patient provided informed consent for the publication of their clinical data.

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